Guidelines to Diagnosis and Monitoring of Fabry Disease and Review of Treatment Experiences

Ana Maria Martins, MD, PhD, Vânia D'Almeida, MD, Sandra Obikawa Kyosen, MD, Edna Tiemi Takata, MD, Alvimar Gonçalves Delgado, MD, PhD, Ângela Maria Barbosa Ferreira Gonçalves, MD, Caio César Benetti Filho, MD, Dino Martini Filho, MD, Gilson Biagini, MD, Helena Pimentel, MD, Hugo Abensur, MD, PhD, Humberto Cenci Guimarães, MD, Jaelson Guilhem Gomes, MD, José Sobral Neto, MD, PhD, Luiz Octávio Dias D'Almeida, PhD, Luiz Roberto Carvalho, MD, Maria Beatriz Harouche, MD, Maria Cristina Jacometti Maldonado, MD, Osvaldo J. M. Nascimento, PhD, Paulo Sergio dos Santos Montoril, MD, and Ricardo Villela Bastos, MD

Fabry disease (MIM 301500) is an inborn error of metabolism characterized by a deficiency in the activity of the lysosomal enzyme α-galactosidase A (α-Gal A), an enzyme involved in the catabolism of glycosphingolipids (Figure). The deficiency leads to progressive accumulation of mainly globotriaosylceramide (GL-3 or Gb3) and, to a lesser extent, of galabiosylceramide, particularly in lysosomes of vascular endothelial cells, renal cells, neural cells, and cardiomyocytes.[1] Gradually, tissue and organ damage develops and, with age, organ functions will deteriorate, leading to premature mortality. Men with classic Fabry disease lack α-galactosidase A activity or have virtually undetectable levels, causing onset of symptoms in childhood or adolescence and, in adulthood, renal, cardiac, and severe cerebrovascular complications.

The inheritance pattern is X-linked, but current data confirm that female heterozygotes may become as severely affected as males, although generally at a later age.[2-4] Atypical manifestations may occur in males (atypical variants), with manifestations more or less confined to 1 organ system (kidneys or heart) and later onset.[1,5]

Reported estimates of the incidence of Fabry disease range from 1 in 40 000 males[1] to 1 in 117 000 in the general population.[6] Specific incidence data for the Brazilian population are not available, but we expect the incidence not to be different from these reported estimates, given the pan-ethnic distribution of this disorder.

Historical Background

In 1898, independent from each other, 2 dermatologists (William Anderson in England, and Johannes Fabry in Germany) first reported on patients with "angiokeratoma corporis diffusum."[7,8] In 1947, the observation of abnormal vacuoles in blood vessels throughout the body at post mortem examination in 2 patients who had died from renal insufficiency led to the recognition of this disease being a generalized storage disorder.[9] The fatty nature of the stored material was proven,[10] and, in 1953, the first living patient was diagnosed by demonstration of dermal vascular lipid deposits.[11] Fabry disease was classified as a sphingolipidosis in 1963.[12] Subsequently, the inborn lysosomal nature of the disease was recognized,[13] and α-Gal A was identified as the deficient enzyme in Fabry disease.[14] In the 1970s, the first trials that focused on the replacement of the deficient enzyme were conducted[15-17] and, after decades of dedicated research, recombinant production techniques[18] allowed production of human α-Gal A in a Chinese hamster ovary host cell line in the 1990s.

Genetics, Inheritance, and Genetic Counseling

After the localization of the *GLA* gene to the Xq22.1 region[19] and identification of the first *GLA* mutation in 1989,[20] improvements in methods of analysis have resulted in identification of a wide variety of molecular alterations. To date, more than 400 mutations have been reported in the Human Gene Mutation Database (www.uwcm.ac.uk/uwcm/mg/hgmd0.html), including mutations in codifier regions, defects in RNA processing, gene rearrangements, small insertions and deletions, and complex mutations. The majority of mutations are private mutations, in other words, family-specific

α-Gal A	α-Galactosidase A
CKD	Chronic kidney disease
eGFR	Estimated glomerular filtration rate
ERT	Enzyme replacement therapy
GLA	*α-Galactosidase A* gene
GL-3	Globotriaosylceramide
GL-2	Lactosylceramide
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
LV	Left ventricular
LVH	Left ventricular hypertrophy
RV	Right ventricular
SSCP	Single-strand conformational polymorphism

From the Centro de Referência em Erros Inatos do Metabolismo (A.M.M., V.D., S.O.K., E.T.T.), Universidade Federal de São Paulo, Brazil; Universidade Federal do Rio de Janeiro (A.G.D.), Rio de Janeiro, Brazil; Clínica de Dermatologia (A.M.B.F.G), RS; Unureste Presidente Prudente (C.C.B.F.), São Paulo, Brazil; Hospital Beneficiência Portuguesa (D.M.F.), São Paulo, Brazil; Hospital São Lucas de Curitiba (G.B.); APAE de Salvador (H.P.); Universidade de São Paulo (H.A.), São Paulo, Brazil; Clínica Censi Guimarães (H.C.G.), Sorocaba, São Paulo, Brazil; Instituto de Hemodiálise de Sorocaba (J.G.G.), São Paulo, Brazil; CentroCard (J.S.N.), Brasília; Hospital Regional Araruama (L.O.D.D.); Hospital São Vicente de Paula (L.R.C.), Passo Fundo; Universidade Federal Fluminense (M.B.H.); Pam Heliópolis (M.C.J.M.), São Paulo, Brazil; Universidade Federal Fluminense (O.J.M.N.); Centrocor (P.S.d.S.M.), Belém; Universidade Federal de Juiz de Fora (R.V.B.), Juiz de Fora, Brazil

Please see Author Disclosures section at the end of this article.

0022-3476/$ - see front matter. 10.1016/j.jpeds.2009.07.003

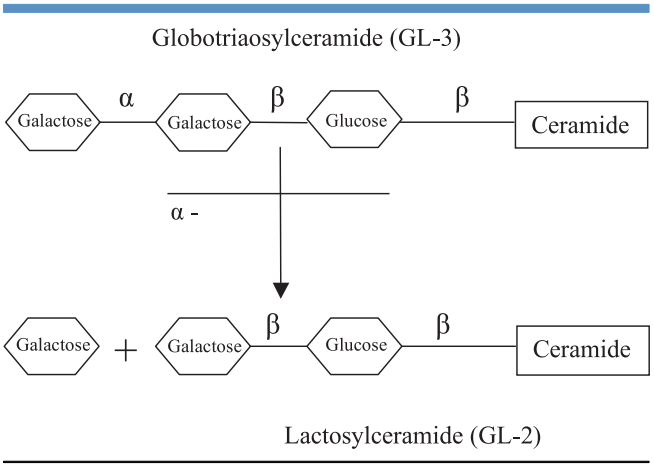

Figure. Role of α-galactosidase A in GL-3 catabolism.

mutations, whereas those repeating in more than 1 family tend to occur in CpG dinucleotides.[21,22] Absence of a family history does not rule out Fabry disease as de novo mutations may occur.[1] Characterization of mutations in Fabry disease is vital because it allows calculation of frequencies and determination of the nature of mutations and improves knowledge about genotype-phenotype correlations.

Inheritance of Fabry disease follows an X-linked pattern. The vast majority of males carrying the hemizygous gene present the classic form of the disease. Females, however, are also at risk of developing disease manifestations (see also "Clinical Manifestations in Female Heterozygotes"). The diverse expression found in heterozygote women presumably results from skewing of X-chromosome inactivation. X-chromosome inactivation takes place in every cell at the start of embryogenesis.[3,23] Heterozygotes for enzymatic deficiencies linked to the X chromosome present 2 lineages of cells; 1 with the mutant gene and 1 cell line with normal cellular enzymatic activity. The ratio of affected and nonaffected cells in bodily tissue mosaics is close to 50:50, but, due to the random choice, the proportions of these cell types may vary considerably between females as well as between tissues.

Genetic counseling is essential after the diagnosis has been established. The patients and families should be provided with information about the course of the disease and therapeutic options. Parents should be informed about the likelihood that siblings, relatives, and future children will inherit the disease. Affected mothers have a 50% chance of passing the defective gene on to all offspring whether boys or girls. Sons who inherit the gene will be affected; her daughters may display a spectrum of clinical involvement. Fathers with Fabry disease pass on the defective gene to none of their sons and all of their daughters. Previously, unrecognized family members, males and females, can be identified at an early stage of the disease via screening for the mutation among family members.[24] Currently, prenatal diagnosis can be established in boys via α-Gal A deficiency testing using chorionic villi or cultured amniocytes. If the family mutation is known, prenatal diagnosis may be obtained by molecular analysis, both in boys and girls.[25]

Pathology

Fabry disease is primarily a small-vessel disease, and lesions are present in virtually all organs and tissues including the blood vessels, kidneys, heart, central nervous system, gastrointestinal tract, spleen, lung, lymph nodes, skin, and sweat glands.[1] Accumulation of GL-3 in vascular endothelial cells represents the initial insult and the cascade of secondary responses result in ischemic tissue damage due to a combination of luminal encroachment and occlusion of vessels, derailment of the balance between vasodilatative and vasoconstrictive mechanisms, and thrombotic and thromboembolic events.[26,27]

The early symptoms mostly result from loss of function of neuronal cells in the somatosensory and autonomous nervous systems due to GL-3 accumulation in the vasa vasorum of small myelinated and unmyelinated fibers.[28-30] Endothelial GL-3 storage can be found in perineural and endoneural vessels, Schwann cells and posterior root ganglions, and in cerebral and cerebellar vessels, particularly those of the carotid-basilar system.[1,31,32] Abnormal pain thresholds result from GL-3 deposition in dorsal root ganglia.[28,33] The origin of auditory alterations is most likely multifactorial, for example, GL-3 accumulation within cochlear nerve cells and smooth muscle cells and atrophy of the stria and spiral ligament.

A skin biopsy specimen may show large electrodense lipid deposits in endothelial, pericyte, and fibroblast cells, in erector muscles, in secretory, canalicular, and myoepithelial cells of the eccrine glands, and in the external sheath of the pilary follicles causing structural deformities in the hair shaft.[34,35] Despite the absence of angiokeratoma, cutaneous biopsy is likely to reveal dermal deposits.

Deposits are seen in the vascular endothelium of mesenteric blood vessels and in small unmyelinated neurons and ganglion cells, particularly in the Meissner plexus.[36]

Renal biopsy specimens show pathognomic structural alterations with deposition in podocytes, mesangial cells, glomerular endothelial cells, Bowman membrane, distal tubular cells, arterial and arteriolar smooth muscle cells, vascular endothelial cells, and interstitial cells.[37,38]

A variety of cardiac lesions may be demonstrated including GL-3 accumulations in vascular endothelial cells, cardiomyocytes, smooth muscle cells, conduction system cells, and valvular fibrocytes.[39,40]

Brain alterations result from lipid deposits that can be found in the sympathetic ganglions of the autonomic nervous system, brainstem, hypothalamus, amygdala, hippocampus, and in the entorhinal cortex.[41,42]

In pulmonary lesions, deposits are found in arterial vessels, pneumocytes and epithelial cells of the bronchial membrane.[43]

Autopsy findings have demonstrated lipid deposition in the interstitium of the testicular parenchyma (Leydig cells), peritubular myoblasts, and deposits in vascular endothelium and perivascular cells.[1] Similar deposits were found in epithelial cells of the efferent and epididymis ducts.[44]

Clinical Manifestations

Neurological Manifestations

Patients with Fabry disease present peripheral and central manifestations. Neuropathic pain is often the first manifestation of loss of small, unmyelinated nerve fiber function and can present in 2 forms.[29,30] Acroparesthesia are described as chronic "burning" on soles of the feet and hand palms and episodes of intense neuropathic pain originating in the hands and feet with proximal radiation. Episodes may last for days or weeks and are generally accompanied by fever and elevated erythrocyte sedimentation rate. These episodes ("Fabry crises") may be triggered by physical activity, heat, stress, or temperature changes, as patients are not able to lower their body temperature by sweating. Unfortunately, acroparesthesias are often misdiagnosed as growing pains or malingering. Recurrence of pain coupled with absence of a diagnosis can lead to patients becoming depressed in adulthood.[45]

Peripheral neuropathy also manifests as autonomic dysfunction causing hypohidrosis or anhidrosis (inability to sweat), orthostatic hypotension, and bowel disturbances (diarrhea, postprandial pain/bloating, nausea, vomiting).[46] Sensory losses, especially loss of thermal sensation, due to autonomic dysfunction and loss of small peripheral sensory neurons, are particularly prominent.[29,30]

The major pathology in the central nervous system includes ischemic and/or hemorrhagic cerebrovascular accidents, transient ischemic attacks, and white matter lesions.[47,48] Hemiparesis, paraparesis or monoparesis, hyperflexia, ataxia, vertigo or dizziness, and complications secondary to vascular alterations (eg, diplopia, dysarthria, nystagmus, hemiataxia, and memory deficits) may develop. Cranial nerve damage may cause ophthalmoplegia, neuralgia of the trigeminus, peripheral facial paralysis, neurosensorial deafness, dysphagia, and cervical plegia.[49,50]

Depending on the location of the central nervous system lesions, other neurologic syndromes may present including frontal lobe syndrome with disturbances in behavior and/or memory and movement abnormalities.

Cerebral involvement can be detected by MRI, as multiple lesions are located in the deep white matter (a particularly vulnerable area because of the blood supply via long penetrating arteries) and in the subcortical grey matter of both hemispheres.[47,51] The posterior cerebral artery territory seems susceptible to vascular lesions and perfusion disturbances.[48]

Patients with Fabry disease are at risk of developing auditory-vestibular abnormalities. Progressive hearing loss of sensorineural origin, particularly for high-frequency sounds, sudden deafness (due to cochlear vascular occlusion), tinnitus aurium, and vertigo are common.[49,52,53] A survey in a large cohort of patients revealed auditory symptoms in 56% of the patients, but clinically relevant hearing impairment was detected in only 16%.[54]

Dermatologic Manifestations

Cutaneous lesion is a common feature and may first be noticed in childhood (boys) or adolescence (girls) usually in the area between the umbilicus and the knees.[55,56] With age, the reddish purple, nonblanching vascular lesions progressively increase in number and size. Hair may be become thicker with a coarse texture.[1]

Although angiokeratomas are often regarded as being synonymous with Fabry disease, they may also be present in patients with other enzymatic deficiencies, for example, in patients with fucosidosis.[57]

Ophthalmologic Manifestations

Generally, ocular lesions do not affect vision.[58] Corneal opacities are the most characteristic ophthalmologic feature occurring in virtually all males and in the majority of heterozygous females.[25,59] Superficial diffuse corneal haziness gradually evolves into spiral streaks in the corneal epithelium ("cornea verticillata") detectable upon slit-lamp examination. Corneal verticillata is not pathognomonic for Fabry disease because it may also be encountered in patients using phenothiazine, chloroquine, indomethacin, or amiodarone.[1,60] The opacities are believed to be caused by accumulation of glycosphingolipids at the level of the Bowman layer and anterior stroma.

Narrowing of arterioles, dilation of veins, exaggerated tortuosity of retinal and conjunctival vessels, and capsular deposits in the anterior or posterior lens may occur, particularly in males.[59,61,62]Central retinal artery occlusion [62,63] and ischemic optic neuropathy[64] are rare.

Renal Manifestations

Renal involvement may occur as early as in childhood or adolescence, and first signs include microalbuminuria, impairment in urinary concentration ability, and lipiduria.[37,65] Polarization microscopy of urinary sediment may show the characteristic birefringent lipid globules ("Maltese crosses") and desquamated tubular cells.[1] Similarly to that seen in diabetic nephropathy, glomerular hyperfiltration may occur at an early stage.[37] Rapid onset of kidney failure occurs if a critical number of nephrons has been damaged.[25] Progressive decline in renal function generally becomes apparent in the 3rd or 4th decade of life and results from damage secondary to GL-3 accumulation in vascular endothelium and renal cells (eg, interstitial scarring, glomerulosclerosis, tubular atrophy).[1,66] Males with the classic form of Fabry disease progress to end-stage renal disease and, if untreated, the average life expectancy is severely reduced to approximately 50 years.[66] Rates of decline of estimated glomerular filtration rate (eGFR) up to −12.2 mL/min/y have been found in patients with chronic kidney disease (CKD) stage 3 who reached end-stage renal disease, versus overall annual rates of −4 mL observed in other nephropathies.[67]

A comprehensive analysis of renal data from 1262 untreated patients (54% females, 46% males) enrolled in the Fabry Registry confirmed that Fabry nephropathy is more prevalent and heterogeneous than previously thought, both in males and females.[68] A significant proportion of females had progressed to moderate to severe kidney involvement occurring at the same mean age as in males.

Albuminuria, proteinuria, and chronic kidney disease are common elements of a progressive Fabry nephropathy.[68] In patients over 40 years of age, 45% of males and 20% of females had an eGFR <60 mL/min/1.73 m^2. Overt proteinuria (>300 mg/24 h) was found in 43% of males and 26% of females with CKD stage 1. Both in males and females, the prevalence and magnitude of proteinuria was higher in those in more advanced stages of kidney disease. Of CKD stage 1-2 patients without overt proteinuria, 55% of males and 35% of females had albuminuria >30 mg/24 h. Thus, albuminuria may be an even more sensitive early marker of progression of renal disease than proteinuria. Proteinuria values were significantly correlated with systolic blood pressure in both sexes.

Renal outcome in patients receiving enzyme replacement therapy (ERT) appears to be related to the degree of interstitial fibrosis and glomerular scarring. Patients who demonstrated renal progression during the Phase 3 extension clinical trial with agalsidase-β shared a common clinical profile, including age >40 years, significant baseline proteinuria (>2 g/24 h), and >50% glomerular sclerosis at pretreatment.[69]

Cardiovascular Manifestations

With age, cardiovascular anomalies increase in severity, more often and earlier in males than in females,[70] and become a key cause of morbidity.[71]

The earliest findings include sinus node dysfunction and conduction system abnormalities. Shortening of the P-R interval is seen in young patients, and later, atrio-ventricular blocks and sinus node dysfunction may develop. Arrhythmia (eg, bradycardia, ventricular tachycardia) can result in sudden death.[40,72] Late signs and symptoms include arterial hypertension due to renal insufficiency and vascular Fabry pathology, and angina pectoris. Myocardial infarction resulting from involvement of the coronary vascular bed, predominantly of the small penetrating vessels, congestive heart failure, and heart failure, are additional serious complications.[39]

Concentric left ventricular hypertrophy (LVH) with diastolic dysfunction is a common feature, more so in males than in females. Studies have shown that 3% to 12% of patients with unexplained LVH actually had Fabry disease.[73,74] Although global systolic dysfunction is rare, regional systolic abnormalities can be detected using modalities such as strain rate imaging.[75,76] Of the valvulopathies, mitral insufficiency occurs most frequently.

Results from Fabry Registry analyses indicate that left ventricular mean wall thickness increases progressively with decreasing renal function in both male and female patients.[70] In addition, interstitial myocardial fibrosis appears to be correlated with progression of renal insufficiency.[77,78] Findings from contrast MRI studies and strain rate Doppler studies indeed show that myocardial fibrosis (gadolinium late enhancement in the basal inferolateral LV wall) is a determining factor of cardiac dysfunction in patients with Fabry disease.[76,79]

Lymphedema, particularly of the lower extremities, may occur in classically affected patients and presumably reflects derailment of the balance between vasodilatative and vasoconstrictive mechanisms.[80]

Pulmonary Involvement

Pulmonary complications (eg, chronic cough, dyspnea with exercise, wheezing) may present in adulthood.[43,81] Obstructive disease is presumably caused by GL-3 accumulation in epithelial and smooth muscle cells hampering air flow. Exercise intolerance is attributed to hypohidrosis, pulmonary disease, or cardiomyopathy and may begin in childhood.[82] Reduction in spirometric parameters corresponding to mild to severe airway obstruction has been observed in 26% of females and 61% of male patients.[83]

Gastrointestinal Involvement

Gastrointestinal symptoms, partly due to gastric emptying difficulties, lead to significant morbidity and are commonly present in childhood, both in boys and girls, with abdominal pain and diarrhea being most frequent.[55,72,84] Early satiety, postprandial bloating, nausea, and vomiting also occur frequently. Symptoms worsen with advancing age. Acute abdominal pain can mimic appendicitis or renal colic.[1]

Rheumatologic and Vascular Manifestations

Vasospastic disturbances characterized by episodes of changes in color of fingers and toes (Raynaud phenomenon), accompanied by paresthesias and pain triggered by temperature changes do occur as early as in childhood.[72]

Joint pain accompanied by fever may occur in hands and feet (interphalangeal, metacarpophalangeal, metatarsal joints)[1] and is frequently misdiagnosed as rheumatic fever, or rheumatoid or juvenile arthritis.[85] Patients may also report pain in the elbows, shoulders, or knees. The underlying cause may be ischemia due to GL-3 deposition in the vascular or neuropathic endothelium at nerve endings of joint structures

Muscle pain may contribute to the limitation in exercise tolerance, together with hypohidrosis, pulmonary disease, and cardiomyopathy.[82]

Morphological characteristics of the face (eg, periorbital fullness, bushy eyebrows, recessed forehead, shallow midface, coarse features, finger deformities) may be found in young males.[86,87]

Avascular necrosis of the femur head and talus may occur, along with osteolytic lesions to the femur head.[88] Osteopenia has been reported in a major fraction of patients,[89,90] and growth retardation and delayed puberty are not uncommon.[1]

Patients with Fabry disease are at risk of developing thrombotic and thromboembolic complications due to the generalized prothrombotic or inflammatory state and endothelial dysfunction.[26,27]

Psychosocial Aspects

The pain in Fabry disease leads to fundamental changes in the quality of life of both the patient and family. Perception of painful stimuli can be modified quantitatively and qualitatively depending on a series of factors relating to the individual or the environment. In the case of acute pain, the perception acts as a signal that induces the person to adopt a behavior which aims at warding off, reducing or

eliminating the cause of the pain. These reactions are significantly influenced by past experiences, sociocultural context, amid which lesions and pain occur, and by the psychological state.

Chronic pain and subsequent alterations in behavior of sufferers can be influenced by environmental factors. When the environment positively reinforces the painful behavior, this tends to persist even in the absence of stimuli.

Shortly after diagnosis and genetic counseling, the patient may express shock, anger, denial, feeling of being cheated, depression, and or acceptance of the new situation; therefore the patient should be constantly monitored as patients are prone to become chronically depressed.[45,91-93]

Clinical Manifestations in Female Heterozygotes

The conception of the expression of Fabry disease in females has drastically changed over the last decade. Studies have clearly shown that the disease is not limited to manifestations in males only.[2-4]

Disease expression in females is variable, and clinical phenotypes range from asymptomatic patients to women with disease manifestations as severe as observed in classically affected males. Clinical variability does not apply merely to severity of symptoms but also to the range of tissues affected and onset of symptomatology. Onset of first symptoms and adulthood complications generally occur at a later age as compared with males.[2-4]

The main first manifestations described in obligate heterozygous women include acroparesthesia, gastroenterological disturbances, hypohidrosis, corneal opacities, and, slightly less frequent, angiokeratoma, mainly on the breasts, lips, and trunk. Disabling and life-threatening renal, cardiac, and cerebrovascular manifestations also occur in heterozygous females.[2-4,68] For females with renal progression, a median age at occurrence of 38 years has been reported.[55] Onset of cerebrovascular and cardiovascular events occurred at a median age of 43 and 47 years, respectively, thus later than in males (age, 38 and 41 years, respectively).

Clinical Manifestations in Childhood

GL-3 deposits have been found in placental tissue, which suggests that extensive storage is already present at birth.[94,95] However, children typically are not symptomatic in the first years of life. Patients usually present in childhood or adolescence with symptoms reflecting progressive loss of function of small, unmyelinated nerve fibers of the somatosensory and autonomous nervous systems.[28] First symptoms may include chronic neuropathic pain and/or acute pain attacks; lack of or decreased sweating; tinnitus; heat, cold, and exercise intolerance; gastrointestinal disturbances (eg, diarrhea, abdominal discomfort, nausea, vomiting); and difficulty gaining weight. Furthermore, skin lesions (angiokeratomas), corneal opacities with unaffected vision, and discrete proteinuria (in male adolescents), are among the first manifestations.[2,25,55,96] These symptoms generally cause significant morbidity despite the absence of major organ dysfunction and are likely to significantly diminish the patient's quality of life and performance. In contrast to other lysosomal disease, Fabry disease is not associated with mental retardation or other evident physical alterations.

Onset of symptoms has been reported to occur at a mean age of 9 years in boys and 13 years in girls.[55,96]

Fabry Disease Characteristics in the Brazilian Patient Cohort

Our analyses (June 2008, unpublished) of natural history data from Brazilian patients with Fabry enrolled in the Fabry Registry, a voluntary observational database, confirm that symptoms generally present at pediatric age in both males and females.

Among the 53 male (median age, 38 years) and 56 female (age, 34.5) patients, the median age of symptom onset was 9 and 11 years, respectively. Symptoms at presentation most often included neurologic pain (83% of males, 64% of females), angiokeratoma (17%, 4%), gastroenterologic disturbance (4%, 2%), eye abnormality (0%, 7%), and renal (9%, 2%), cardiovascular (4%, 4%), and cerebrovascular abnormalities (2%, 4%). The most common first symptoms were reported at the following median ages: neurologic pain at 9 and 11 years for males and females, respectively, angiokeratoma at 9 and 19.5 years, and renal abnormalities at 12 and 14 years, respectively.

The ages at first major clinical renal (dialysis, transplantation), cardiovascular (significant cardiac procedure, arrhythmia, angina pectoris, congestive heart failure, signs of left ventricular hypertrophy on ECG) or cerebrovascular events (transient ischemic attack, stroke) were 40 (n = 13) and 37 (n = 1), 44.5 (n = 8) and 43 (n = 5), and 39.5 (n = 6) and 44.5 (n = 2) years for males and females, respectively. Although fewer female patients with Fabry disease had major clinical events, the ages at which clinical events occurred appear to be quite similar in both sexes.

Diagnosis

Symptoms are usually present in childhood or adolescence but, at onset, are usually subtle and resemble symptoms of more common diseases. Many patients are initially misdiagnosed (Table I), and delays between onset and accurate diagnosis exceeding 10 years have been reported in both sexes.[55,96] Also in the Brazilian cohort of patients, there were significant delays in diagnosis. Although first symptoms generally presented during childhood, diagnosis occurred at a median age of 32.5 years in males and 27 years in females. If a carefully taken medical history, physical examination, laboratory tests, and imaging procedures trigger the suspicion of Fabry disease, the diagnosis should be confirmed by analysis of α-Gal A activity and, particularly in females, by molecular analysis.

Biochemical Diagnosis

The biochemical diagnosis of Fabry disease is established by measuring α-Gal A. activity in plasma or leukocytes taken from peripheral blood, cultured fibroblasts,[97] or using samples extracted from filter paper blood spots.[98]

Measurement of α-Gal Activity in Cultivated Fibroblasts, Plasma, or Leukocytes. In males, the measurement of α-Gal A in cultivated fibroblasts, plasma, or leukocytes in peripheral blood is the preferred method for the biochemical diagnosis.

A 5-mL (for plasma) or 10-mL (for leukocytes) volume of blood is collected in a syringe containing heparin or by using a heparinized tube. Plasma is obtained by centrifuging the sample at 2000 rpm for 10 min at 4°C, and leukocytes are separated from the blood.[99] This material can be stored at −40°C until further analysis. The fibroblasts are cultured from a skin biopsy generally obtained from the forearm by an aseptic surgical technique.[100]

Measurement of α-Gal A is performed as outlined by Desnick et al.[101] Samples of cultivated fibroblasts, plasma, or leukocytes are added to an incubation medium containing 4-Methylumbelliferyl β-D-glucopyranoside substrate in citrate-phosphate 50 mM pH 4.8 buffer. This mixture is incubated at 37°C for 2 hours in an agitated warm water bath. Subsequently, the reaction is terminated by adding glycine-NaOH 0.5 M, pH 10.3 buffer, and fluorescence is measured by spectrofluorometry with a standard curve of 4-methylumbelliferone (365-nm excitation and 450-nm emission). For leukocytes and fibroblasts, the protein level of the sample must be determined as the result is expressed as nanomoles of hydrolyzed substrate per hour per milligram of protein. If plasma is used, enzymatic activity is expressed as nanomoles of hydrolyzed substrate per hour per milliliter of blood. Men with classic Fabry disease lack α-Gal A activity or have virtually undetectable levels. Female heterozygotes, however, even if they are symptomatic, can present values within the normal range. Molecular analysis should be performed to establish the diagnosis in these cases.[102]

Table I. Fabry disease: Common misdiagnoses

Medical specialty	Misdiagnosis	Fabry symptom/sign
Neurology	Multiple sclerosis	Stroke (MRI)
	Chronic intermittent polyneuronopathy	Pain, tingling in hands and feet
	Raynaud syndrome	Pain and abnormal thermal sensitivity in extremities
	Neurosis/malingering	Unexplained acute pain
Rheumatology	Rheumatoid or juvenile arthritis	Joint pain, increased erythrocyte sedimentation rate
	Rheumatic fever	Pain accompanied by fever and increased erythrocyte sedimentation rate
	Autoimmune disorder/ lupus	Angiokeratomas
	Growing pains	Unexplained pain in limbs
Nephrology	(Glomerulo)nephritis	Renal insufficiency
Cardiology	Carditis	Mitral murmur
	Hypertrophic cardiomyopathy e.c.i.	Hypertrophic cardiomyopathy
Dermatology	Petechiae	Angiokeratoma
Internal Medicine/ Gastroenterology	Vasculitis	Microvascular disease
	Inflammatory bowel disease	Diarrhea, abdominal discomfort, nausea, vomiting
	Appendicitis	Severe abdominal pain in the right iliac fossa
	Renal colic	Severe abdominal pain
Hematology/oncology	Erythromelalgia	Acute pain in extremities

Measurement of α-Gal A Activity in Blood Spot Filter Paper. This technique[98] is useful for screening of a large numbers of patients in populations at high risk of having the disease, including patients on chronic dialysis or patients with unexplained left ventricular hypertrophy or early stroke. The advantages of using this technique include that samples can be easily obtained, stored, and conserved and can be sent without the need for special packing (by regular postal service for instance). In addition, samples can be processed very efficiently, and the method is less expensive and less tedious than leukocyte analysis. However, to produce reliable and reproducible data, care must be taken during the collection of samples.

Blood spots should preferably be taken from a sample drawn from the arm vein. Samples can only be taken from the heel in children under 6 months of age. Upon impregnating the filter paper, the spot should spread evenly filling the whole allocated area. The paper must be dried at room temperature and may only be stored in the refrigerator when completely dry.

The technique for measuring enzyme activity in blood samples by spot filter paper was developed by Chamoles et al,[98] who modified the original analysis method for α-Gal A.[103,104] Paper discs measuring 3 mm across and corresponding to a total of 5.5 μL of blood are used. One disc is placed in each test tube, together with 0.25 mol/L of *N*-acetyl-D-galactosamine (for elution of the sample and inhibition of galactosidase B) and 4-methylumbelliferyl β-D-glucopyranoside substrate (5 mmol/L). After incubation at 37°C in an agitated warm water bath for 20 hours, the reaction is interrupted by the addition of ethylenediamine (0.1 mol/L) and the enzyme activity is measured by quantifying the fluorescence of the 4-methylumbelliferone product (365-nm excitation and 450-nm emission), based on a standard curve. Enzymatic activity is expressed as micromoles of hydrolyzed substrate per liter of blood per hour.

Good reproducibility can be achieved by using this technique, and results for male patients and healthy subjects do not overlap.[98] If abnormal results are obtained, subsequent blood samples allowing separation of plasma and leukocytes, or fibroblasts for cultures should be requested to confirm the biochemical diagnosis and to perform molecular analysis.

GL-3 Levels. GL-3 levels can be assessed in blood and urine samples by chromatography and quantified using high

throughput high-performance liquid chromatography.[105] For both methods, GL-3 must be extracted from the biological sample with a chloroform-methanol mixture. Results from a recent study suggest that the levels of urinary Gl-3 excretion in children and adults with Fabry disease are directly related to the types of genetic mutations.[105]

Molecular Diagnosis. Biochemical analyses can successfully identify the vast majority of affected males and heterozygous females; females may have (near) normal α-Gal A enzyme activity.[25] Asymptomatic patients may be identified through screening of the family of an affected individual.[24] Identification of a specific point mutation in a patient's family members can be carried out by means of restriction enzymes, by probes for specific allele synthetic oligonucleotides, or preferably through DNA sequencing of the gene fragment presenting the alteration.[106] Advances in the development of rapid DNA sequencing tests have dramatically improved the efficiency of mutation identification.

Molecular Analysis. Genomic DNA must be extracted using techniques routinely used in Molecular Biology laboratories, for example, the methodology reported by Miller et al that uses lymphocytes from peripheral blood.[107] Genomic DNA may also be obtained from lymphocytes or tissue biopsies using commercially available kits and following the recommended protocol in the manufacturer's manual.

Once the DNA is available, polymerase chain reaction, as well as sequencing can be performed using previously described techniques.[104,108] Sequencing must cover all 7 exons of the *GAL* gene, which are amplified by polymerase chain reaction using primers (oligonucleotides) designed based on the intronic regions flanking these exons.[19,108] The amplified products are sequenced by dideoxyribonucleoside chain reaction (solid-phase dideoxy chain sequencing), in which carbon dideoxyribonucleoside triphosphates do not present hydroxyl in the 3′ carbon; once incorporated, they prevent addition of another nucleotide, thus terminating chain elongation.[109] Automated sequencing has also been used, as well as a series of other techniques capable of identifying molecular alterations, such as single-strand conformational polymorphism analysis (SSCP), and mismatch analysis by fluorescence, among others.

Detailed recommendations for the clinical evaluation and monitoring of the disease status in pediatric and adult patients with Fabry disease (receiving ERT or treatment-naïve) are presented in **Tables II** and **III**.

While taking the medical history, inquire about manifestations suggestive of neurologic symptoms (hemorrhagic cerebrovascular accident; transient ischemic attack; memory loss; headache; decreased ability to sweat; heat or cold intolerance; chronic pain or recurrent episodes of pain requiring medication and frequency; abdominal pain or diarrhea and frequency), arrhythmia, myocardial infarction, angina, hypertension, and cardiac insufficiency. If patients report symptoms, inquire if symptoms are stable, have improved, or have worsened.

At physical examination, besides measurement of weight, height, blood pressure, and assessment of systems, check for presence or worsening of angiokeratomas.

The battery of tests includes assessment 24-hour microalbuminuria, proteinuria, and creatinine clearance. Renal biopsy should be considered in those patients with microalbuminuria to assess kidney involvement, which may provide information on prognosis and response to treatment.

Hypertrophic myocardiopathy can be demonstrated noninvasively by echocardiography. Assessments include interventricular septum and LV posterior wall thickness, ventricular mass (LVH if >130 g/m^2 in men and >110 g/m^2 in women), LV systolic and diastolic functions, degree and distribution of hypertrophy, and mitral valve function. Radiography of the thorax generally does not reveal specific findings. Arrhythmias can be diagnosed by 24-hour Holter monitoring. Nuclear magnetic resonance imaging enables detection of focal myocardial fibrosis and identification and quantification of ventricle hypertrophy. Left ventricular and end-diastolic pressures and quantification of the degree of mitral regurgitation can be assessed by hemodynamic studies. New cardiac imaging techniques (tissue Doppler imaging) appear to be more sensitive than conventional echocardiography and can identify LV radial and longitudinal dysfunction before LVH develops.

Routine motor and nerve conduction studies typically measure large fiber function and are generally not useful as large myelinated nerve fibers have minimal lipid storage.[28] Electroneuromyography may detect alterations compatible with diffuse axonal lesion. Quantitative sensory tests for warm, cold, and heat pain perception thresholds are usually abnormal. In addition, tests of vibratory perception, sudomotor and sweat gland function, and limb and superficial skin blood flow and vasoreactivity can effectively measure the extent of neurological dysfunction.[29,30,110] Sural nerve biopsy may demonstrate lipid deposits and

Table II. Clinical evaluation and monitoring of pediatric patients with Fabry disease

Assessment	Recommended schedule
Clinical assessment	At diagnosis, annually through medical history and full physical examination
Neurologic examination	At diagnosis, annually
Blood chemistry, cholesterol (total, LDL, HDL), triglycerides, serum creatinine	At diagnosis, annually
24-hour microalbuminuria, proteinuria	At diagnosis, annually
Creatinine clearance	At diagnosis, annually for adolescents
Echocardiogram, electrocardiogram	Every 2 years for adolescents
Magnetic nuclear resonance of kidneys, heart, brain	At baseline, and subsequently to monitor disease progression and treatment efficacy
Pain and quality of life questionnaire	At diagnosis, annually

Table III. Clinical evaluation and monitoring of adult patients with Fabry disease

Assessment	Recommended schedule	
	Not on enzyme replacement therapy	On enzyme replacement therapy
Clinical assessment	At diagnosis, annually with medical history and full physical examination	6-monthly with medical history and full physical examination
Neurologic examination	At diagnosis, annually (including screening for clinical signs of depression)	6-monthly (including screening for clinical signs of depression)
Brain tomography or magnetic nuclear resonance	At diagnosis, annually	Annually
Electrocardiogram, echocardiogram	At diagnosis, annually	Annually
Ophthalmologic assessment	At diagnosis, annually (including slit lamp exam)	Annually (including slit lamp exam)
Pulmonary tests	At diagnosis, annually (spirometry)	Annually (spirometry)
Audiometry	At diagnosis, annually	Annually
Blood chemistry, cholesterol (total, LDL, HDL), triglycerides, serum creatinine	At diagnosis, annually	6-monthly
24-hour microalbuminuria, proteinuria	At diagnosis, annually	6-monthly
Creatinine clearance	At diagnosis, annually	6-monthly
Plasma GL-3	At baseline, annually	6-monthly
Pain and quality of life questionnaire	At diagnosis, annually	6-monthly

significant reduction in myelinated and unmyelinated small fibers.[32]

Auditory-vestibular involvement is often diagnosed late; therefore, it is recommended to perform audiometric tests, regardless of the clinical complaints, at diagnosis.

Regarding the gastrointestinal tract, radiological tests may reveal signs or delayed gastric emptying, loss of the gastrocolic reflex, thickening of the intestinal walls, dilatation, diverticula, reduced peristaltic activity, constipation, and smoothing or loss of colonic haustration.[84,111]

Pulmonary tests may include spirometry function testing (reduced forced expiratory volume in the first second, increased RV),[43,81] cardiopulmonary exercise testing,[82] and radiological studies (hyperinflation).[43,81] Cytologic study of sputum obtained via bronchial washing (typical Fabry lamellar inclusions),[112] and histopathologic study of bronchial biopsy specimen (lipid inclusions in epithelial cells),[112] are rarely required.

Treatment of Patients with Fabry Disease

Before the availability of ERT, treatment for Fabry disease consisted mainly of symptomatic care and nonspecific corrective measures to treat complications, for example, analgesia, stroke prophylaxis, cardiac interventions including pacemaker, dialysis, and kidney transplantation. These alternatives can prolong life in patients with Fabry disease. However, their efficiency is limited because they do not treat the enzyme deficiency (and consequent substrate storage), which is the underlying cause of the disease.

Control of neuropathic pain may be established by administration of phenytoin, carbamazepine, gabapentin, amitriptyline, or nortriptiline.[31] If required, nonhormonal anti-inflammatory drugs or opiate derivatives may be prescribed. Episodes of "Fabry crises" may be prevented by avoiding exposure to extreme temperature changes, particularly during physical exercise, and by keeping the patient well hydrated. Lubricant eye drops can be prescribed if tear production is deficient due to hypohidrosis. Cryotherapy may be considered as symptomatic treatment of the angiokeratomas. Pulmonary therapeutic care should aim at improving obstructive disease, and smoking should be discouraged. Symptoms of delayed gastric emptying may be treated with metoclopromide.[111] Thrombotic and thromboembolic complications may be prevented by administration of low doses of acetylsalicylic acid.[113] Patients with inadequately controlled blood pressure and overt proteinuria should be treated with antiproteinuric agents to control their blood pressure and 24-hour urine protein excretion[114] as proteinuria values have been found to be significantly correlated with systolic blood pressure in both sexes.[68]

As patients are at risk for chronic depression,[45,91-93] referral to a psychiatrist for better assessment of mental health may be required. Psychological follow-up can provide supportive aid for expression of emotions and feelings involved in the acceptance process and adherence to treatment. Observation of signs and symptoms pertinent to the disease along with the extent to which these affect quality of life can lead to greater information and allow interventions that foster-well being, encouraging individuals to recognize their potential.

Agalsidase β-Enzyme Replacement Therapy

Agalsidase β-enzyme replacement therapy (Fabrazyme; Genzyme Corporation, Cambridge, Massachusetts)[115,116] is produced using recombinant DNA technology and is indicated for long-term enzyme replacement therapy for patients with confirmed diagnosis of Fabry disease. Currently, it is the only specific medication for this disease approved in Brazil and by the FDA (Food and Drug Administration).

The safety and efficacy of agalsidase beta therapy have been proven in several preclinical and clinical studies that are summarized below.

Preclinical Studies

In the 1990s, animal studies in α-Gal A knockout mice ("Fabry mice") demonstrated progressive accumulation of GL-3 in these mice.[117,118] Ioannou et al[119] administered various doses of agalsidase-β (0.3, 1.0, 3.0, and 10 mg/kg) to Fabry mice and found that GL-3 was cleared from plasma, liver, heart, and kidneys in a dose-dependent manner. The

finding of re-accumulation of GL-3 after administration of a single dose confirmed the necessity of repeated dosing.

Phase I/II Study

Based on the findings from the preclinical studies, dosing at 0.3, 1.0, and 3.0 mg/kg was investigated in the open-label Phase I/II clinical trial.[115]

One of these 3 doses was given to 15 males with classic Fabry disease, either every 2 weeks or every 2 days. Plasma and endothelial tissue GL-3 levels rapidly and significantly reduced. The infusions were generally well tolerated, and infusion-associated reactions were found to be less frequent at the 1.0 mg/kg dose as compared with the 3.0 mg/kg dose.

The results confirmed the safety and *in vivo* activity of agalsidase-β and provided the basis for the Phase III trial.

Phase III Placebo-Controlled Study

For this trial, a biweekly dose of agalsidase beta of 1.0 mg/kg body wt was chosen because this dose was considered to represent an optimal balance between risk of infusion-associated reactions and GL-3 clearance. The double-blind, randomized, placebo-controlled Phase III clinical trial enrolled 58 patients (56 males, 2 females) who received either agalsidase-β or placebo every 2 weeks for 20 weeks.

Infusions of agalsidase-β at 1 mg/kg resulted in highly significant clearance of GL-3 from the renal capillary endothelium with 69% of the agalsidase-treated patients reaching the 0 end point (no or trace vessel inclusions). Mean heart, skin, and kidney capillary endothelium scores had decreased significantly at 20 weeks of therapy.

Agalsidase-β infusions were generally well tolerated, the most common adverse events being transient mild to moderate chills and fever. Reduction in the infusion rate and the addition of preventive medications controlled these reactions.

Phase III Open-Label Extension Study

All patients from the Phase III study enrolled in the open-label Phase III extension study.[116] Overall, 98% of biopsied patients achieved a 0 score for vascular endothelium in the kidney after 6 or 12 months of agalsidase beta therapy. Zero scores in the heart and skin vasculature were achieved in 75% and 96% of the patients, respectively. Plasma GL-3 levels rapidly normalized in all patients. Kidney function as measured by GFR and serum creatinine remained stable. In addition to GL-3 clearance from endothelial cells in the kidneys, GL-3 was also cleared from renal interstitial cells and mesangial cells and from dermal capillary endothelial cells.[38]

The patients had low pain scores at entry into the double-blind portion of the study, but pain scores (McGill Pain Questionnaire) improved over time for those who reported pain at pretreatment.[69]

The safety profile during the first 6 months of the open-label study was similar to that found in the double-blind study. Overall, immunoglobulin G seroconversion occurred in 88% of the treated patients without an apparent effect on treatment efficacy.[116]

After 54 months of agalsidase-β therapy at 1 mg//kg, sustained renal stabilization was observed.[69] The median eGFR, proteinuria, and serum creatinine levels remained stable and normal. Renal disease progression was observed in a subgroup of 6 patients who shared a profile that predisposed them to progression of renal disease, that is, age >40 years, high baseline proteinuria, and significant pretreatment glomerulosclerosis. The mean rate of decline excluding these 6 patients was -0.4 mL/min per 1.73 m^2/y. GL-3 clearance from plasma, kidney, skin, heart capillary endothelium, and multiple renal cell types observed in the first years of therapy [116,120,121] was maintained.

Most patients (90%) had seroconverted, mostly within 3 months of therapy. Immunoglobulin G titers were independent of treatment response, as evidenced by the sustained responses. The majority of patients had a 4-fold or more reduction in titer from peak measurement, 9 patients demonstrated a plateau, 9 patients had tolerized, and 1 was considered to be a "low responder." Of the 2 females, 1 had tolerized and 1 remained seronegative.

The infusion time could be safely reduced to a mean of approximately 2.5 hours, and many patients could be transferred to home therapy.[69]

Phase IV Clinical Study

The Phase IV, multicenter, double-blind, placebo-controlled trial enrolled 82 adult patients (representing both sexes) with mild to moderate kidney disease.[122] The main objective of this trial was to investigate if agalsidase-β at 1 mg/kg delays the onset of (the composite) clinical outcome of renal, cardiovascular, and cerebrovascular events and death in patients with advanced Fabry disease. The patients (2:1 treatment-to-placebo randomization) were followed for up to 35 months (median, 18.5 months).

Agalsidase-β therapy substantially reduced the risk of progression of Fabry disease to (the composite end point of) major renal, cardiac, or cerebrovascular events, or death. Risk reductions of 53% (whole study group, $P = .06$) and 61% (patients that followed the protocol, $P = .034$) were found in agalsidase-β–treated patients after adjustment for imbalance in baseline proteinuria.

Subgroup analyses showed that the greatest (and highly significant) treatment effects were seen in patients who had milder impairment of renal function at the onset of therapy, as demonstrated by the 81% event rate reduction in the intention-to-treat group with baseline eGFR >55 mL/min per 1.73 m^2 after adjustment for imbalance in baseline proteinuria. Thus, proteinuria proved to be a major risk factor for developing any event as well as renal events, as has been recognized before in diabetic nephropathy.

The treatment was generally safe and well tolerated. Three patients who had positive or inconclusive serum IgE or skin test results were successfully rechallenged.

Transient mild or moderate infusion-associated reactions occurred in 55% of treated patients and declined in frequency over time. Seroconversion occurred in 74% of male patients and 3 of 8 women.

Pediatric Study

The safety and efficacy of agalsidase-β therapy at 1 mg/kg in children were investigated in a 48-week, multicenter, international, open-label study enrolling 14 boys and 2 girls with Fabry disease.[123]

GL-3 deposits in superficial vascular endothelial cells in the skin were completely cleared within 24 weeks, and moderate-to-severe deposits in the deep vascular endothelial cells were cleared or reduced to mild. Median plasma GL-3 levels returned to normal within 1 month of therapy and, at completion of the study, renal function had not deteriorated.

Reports of gastrointestinal symptoms declined steadily, and patient diaries documented significant reductions in school absences. The safety profile in the children was similar to that in adults; infusion associated reactions mainly included rigors, fever, and rhinitis, mostly mild of intensity, and their frequency decreased over time. Seventy-nine percent of the boys seroconverted. After the 8th infusion, the initial slow infusion rate could be incrementally increased to 2.9 hours.

Other Reports of Therapeutic Outcomes with Agalsidase-β

Regarding early symptoms, significant improvement in small nerve fiber function and intradermal vibration receptors with agalsidase-β have been reported.[124] Gastrointestinal symptoms markedly improved in a small group of patients.[125] Abdominal pain and diarrhea improved, gastrointestinal medications could be terminated, and the patients gained weight.

In addition to the nearly complete clearance of GL-3 from the cardiac capillary endothelium in the majority of patients in the Phase III study,[38,116] other beneficial cardiac effects have been reported. Two groups have demonstrated that agalsidase-β therapy can reduce LVH and ameliorate left ventricular stiffness and regional myocardial function,[76,126] although positive responses seem to depend on the severity of cardiac hypertrophy and fibrosis at baseline.[127]

To date, it is not known if agalsidase-**β** therapy can reduce or prevent the central nervous system–related complications associated with Fabry disease.

Agalsidase-β Treatment Recommendations

The late complications of Fabry disease in adults are the main driver of mortality as well as late morbidity. Data from clinical studies indicate that long-term treatment with agalsidase-β at a dose of 1 mg/kg may halt progression of Fabry disease and reduce the risk of serious complications.[69,122] Therefore, we recommend early and incisive treatment of all male adults diagnosed with Fabry disease with agalsidase-β at 1 mg/kg in an attempt to stop or delay progression, to prevent renal, cardiac, or cerebrovascular events, and to improve survival.

In adult females, the decision to initiate agalsidase-β therapy is more complex because disease presentations and progression considerably vary. We recommend agalsidase-β therapy for adult females who have significant symptoms of Fabry disease or evidence of progression of organ involvement. However, further research is needed regarding the optimal time to initiate agalsidase-β therapy in female patients.

As the natural course of Fabry disease in boys and girls varies markedly among individuals, no generalizations can be made about the optimal age at which to begin therapy. The decision to start, to reverse lipid deposition and to reduce (or prevent) the peripheral neurologic symptoms, must be evaluated on a case by case basis by treating physicians.

Experimental Therapies

Therapies for Fabry disease that may become available in the future include substrate inhibition therapy, enzyme enhancement therapy, and gene therapy.[128] Substrate inhibition therapy intends to slow the rate of production of GL-3 that is accumulating as a result of α-Gal A deficiency. Enzyme enhancement therapy has been suggested as an approach to genetic diseases resulting from protein misfolding and/or mistrafficking. Low molecular-weight pharmaceutical chaperones might rescue misfolded or unstable proteins. Gene therapy for Fabry disease is still only in preclinical (animal) studies, and much research is needed, especially in identifying appropriate vectors and translating gene transfer into clinical practice.

Conclusions

Fabry disease is a severe, progressive, and multisystemic disease, with clinical symptoms arising during childhood or adolescence. Progression of Fabry disease is associated with peripheral neurological symptoms (early symptoms), and with renal, cardiac, and cerebrovascular events (late serious complications). The different manifestations reflect disease progression in different organ systems that need to be assessed and monitored independently. If a patient is diagnosed, his or her family should be offered family screening to identify other previously unrecognized patients at an early stage of the disease.

The safety and efficacy of agalsidase-β therapy at 1 mg/kg have been proven in several preclinical and clinical studies and this treatment should not be withheld from adult male patients. In females and children, the case by case decision to initiate agalsidase-β therapy is less straightforward and largely depends on presence of significant symptoms and evidence of progression of organ involvement and must be evaluated on a case by case basis by treating physicians. ■

Author Disclosures

Ana Maria Martins', MD, PhD received travel expenses from Genzyme as part of continuous medical education and grants as coordinator for the Fabry Registry in Brasil (since 2002) and is a member of the International Board of Advisors for the Fabry Registry (from 2007). The following authors have no financial arrangement or affiliation with a corporate organization or a manufacturer of a product discussed in this supplement: Hugo Abensur, MD, PhD, Sandra Obikawa Kyosen, MD, Ricardo Villela Bastos, MD, Edna Tiemi Takata, MD, Caio Cesar Benetti Filho, MD Jaelson Guilhem Gomes, MD, Luiz Octavio Dias D' Almeida, PhD, Angela Maria Barbosa Ferreira Gonçalves, MD, Dino Martini Filho, MD, Humberto Cenci Guimarães, MD, Maria Beatriz Harouche, MD, Maria Cristina Jacometti Maldonado, MD, Osvaldo J.M. Nascimento, PhD, and Paulo Sérgio dos Santos Montoril, MD, Vânia D'Almeida, MD, Gilson Biagini, MD, José Sobral Neto, MD, PhD, Helena Pimentel, MD, Alvimar Delgado, MD, PhD, and Luiz Roberto Carvalho, MD received travel expenses from Genzyme Brazil as part of continuous medical education.

Reprint requests: Dr Ana Maria Martins, Rua Joaquim Antunes, 620/72, CEP 05415-010, São Paulo, SP. E-mail: anamartins.dped@epm.br.

References

1. Desnick R, Ioannou Y, Eng C. Alpha-Galactosidase A deficiency: Fabry disease. In: Scriver CR BA, Sly WS, Valle D, editors. The Metabolic and Molecular Bases of Inherited Disease. 8th ed. New York, NY: McGraw-Hill; 2001. p. 3733-74.
2. Deegan PB, Baehner AF. Barba Romero MA, Hughes DA, Kampmann C, Beck M. Natural history of Fabry disease in females in the Fabry Outcome Survey. J Med Genet 2006;43:347-52.
3. Wang RY, Lelis A, Mirocha J, Wilcox WR. Heterozygous Fabry women are not just carriers, but have a significant burden of disease and impaired quality of life. Genet Med 2007;9:34-45.
4. Wilcox WR, Oliveira JP, Hopkin RJ, Ortiz A, Banikazemi M, Feldt-Rasmussen U, et al. Females with Fabry disease frequently have major organ involvement: lessons from the Fabry Registry. Mol Genet Metab 2008;93:112-28.
5. Nakao S, Kodama C, Takenaka T, Tanaka A, Yasumoto Y, Yoshida A, et al. Fabry disease: detection of undiagnosed hemodialysis patients and identification of a "renal variant" phenotype. Kidney Int 2003; 64:801-7.
6. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. JAMA 1999;281:249-54.
7. Anderson W. A case of "angiokeratoma". Br J Dermatol 1898;10: 113-7.
8. Fabry J. Ein Beitrag zur Kenntnis der Purpura haemorrhagica nodularis (Purpura papulosa haemorrhagica Hebrae). Arch Dermatol Syphilis 1898;43:187-200.
9. Pompen A, Ruiter M, Wyers H. Angiokeratoma corporis diffusum (universale) Fabry, as a sign of an unknown internal disease: two autopsy reports. Acta Med Scand 1947;128:234-55.
10. Scriba K. Zur Diagnostik des Angiokeratoma corporis diffusum Fabry mit cardio-vasorenalem Symptomenkomplex. Verh Dtsch Ges Pathol 1950;34:221.
11. Hornbostel H, Scriba K. Zur Diagnostik des Angiokeratoma corporis diffusum Fabry mit cardio-vasorenalem Symptomenkomplex als posphatidspeicherungskrankheit durch Probeexcision der Haut. Klin Wochenschr 1953;31:68.
12. Sweeley C, Klionsky B. Fabry's disease: classification as a sphingolipidosis and partial characterization of a novel glycolipid. J Biol Chem 1963; 238:3148-50.
13. Hers H. Inborn lysosomal diseases. Gastroenterology 1965;48:625-33.
14. Brady RO. Enzymatic abnormalities in diseases of sphingolipid metabolism. Clin Chem 1967;13:565-77.
15. Brady RO, Tallman JF, Johnson WG, Gal AE, Leahy WR, Quirk JM, et al. Replacement therapy for inherited enzyme deficiency: use of purified ceramidetrihexosidase in Fabry's disease. N Engl J Med 1973;289:9-14.
16. Desnick RJ, Dean KJ, Grabowski G, Bishop DF, Sweeley CC. Enzyme therapy in Fabry disease: differential in vivo plasma clearance and metabolic effectiveness of plasma and splenic alpha-galactosidase A isozymes. Proc Natl Acad Sci U S A 1979;76:5326-30.
17. Mapes CA, Anderson RL, Sweeley CC, Desnick RJ, Krivit W. Enzyme replacement in Fabry's disease, an inborn error of metabolism. Science 1970;169:987-9.
18. Dingermann T. Recombinant therapeutic proteins: production platforms and challenges. Biotechnol J 2008;3:90-7.
19. Kornreich R, Desnick RJ, Bishop DF. Nucleotide sequence of the human alpha-galactosidase A gene. Nucleic Acids Res 1989;17:3301-2.
20. Bernstein HS, Bishop DF, Astrin KH, Kornreich R, Eng CM, Sakuraba H, et al. Fabry disease: six gene rearrangements and an exonic point mutation in the alpha-galactosidase gene. J Clin Invest 1989;83:1390-9.
21. Ashton-Prolla P, Tong B, Shabbeer J, Astrin KH, Eng CM, Desnick RJ. Fabry disease: twenty-two novel mutations in the alpha-galactosidase A gene and genotype/phenotype correlations in severely and mildly affected hemizygotes and heterozygotes. J Investig Med 2000;48:227-35.
22. Topaloglu AK, Ashley GA, Tong B, Shabbeer J, Astrin KH, Eng CM, et al. Twenty novel mutations in the alpha-galactosidase A gene causing Fabry disease. Mol Med 1999;5:806-11.
23. Lyon MF. Some milestones in the history of X-chromosome inactivation. Annu Rev Genet 1992;26:16-28.
24. Laney DA, Fernhoff PM. Diagnosis of Fabry disease via analysis of family history. J Genet Couns 2008 Jan 3 [Epub ahead of print].
25. Desnick RJ, Brady RO. Fabry disease in childhood. J Pediatr 2004;144: 20-6.
26. Altarescu G, Moore DF, Pursley R, Campia U, Goldstein S, Bryant M, et al. Enhanced endothelium-dependent vasodilation in Fabry disease. Stroke 2001;32:1559-62.
27. DeGraba T, Azhar S, Dignat-George F, Brown E, Boutiere B, Altarescu G, et al. Profile of endothelial and leukocyte activation in Fabry patients. Ann Neurol 2000;47:229-33.
28. Dutsch M, Marthol H, Stemper B, Brys M, Haendl T, Hilz MJ. Small fiber dysfunction predominates in Fabry neuropathy. J Clin Neurophysiol 2002;19:575-86.
29. Low M, Nicholls K, Tubridy N, Hand P, Velakoulis D, Kiers L, et al. Neurology of Fabry disease. Intern Med J 2007;37:436-47.
30. Moller AT, Jensen TS. Neurological manifestations in Fabry's disease. Nat Clin Pract Neurol 2007;3:95-106.
31. Schiffmann R, Scott LJ. Pathophysiology and assessment of neuropathic pain in Fabry disease. Acta Paediatr 2002;91:48-52.
32. Toyooka K, Said G. Nerve biopsy findings in hemizygous and heterozygous patients with Fabry's disease. J Neurol 1997;244:464-8.
33. Kolodny E, Pastores G. Anderson-Fabry disease: extrarenal, neurologic manifestations. J Am Soc Nephrol 2002;13:150-3.
34. Lao LM, Kumakiri M, Mima H, Kuwahara H, Ishida H, Ishiguro K, et al. The ultrastructural characteristics of eccrine sweat glands in a Fabry disease patient with hypohidrosis. J Dermatol Sci 1998;18:109-17.
35. Tabata H, Yamakage A, Yamazaki S. Hair abnormality of Fabry disease. Int J Dermatol 1996;35:576-8.
36. Sheth KJ, Werlin SL, Freeman ME, Hodach AE. Gastrointestinal structure and function in Fabry's disease. Am J Gastroenterol 1981;76: 246-51.
37. Sessa A, Meroni M, Battini G, Maglio A, Brambilla PL, Bertella M, et al. Renal pathological changes in Fabry disease. J Inherit Metab Dis 2001; 24:66-70.

38. Thurberg BL, Rennke H, Colvin RB, Dikman S, Gordon RE, Collins AB, et al. Globotriaosylceramide accumulation in the Fabry kidney is cleared from multiple cell types after enzyme replacement therapy. Kidney Int 2002;62:1933-46.
39. Kampmann C, Wiethoff CM, Perrot A, Beck M, Dietz R, Osterziel KJ. The heart in Anderson Fabry disease. Z Kardiol 2002; 91:786-95.
40. Linhart A, Magage S, Palecek T, Bultas J. Cardiac involvement in Fabry disease. Acta Paediatr Suppl 2002;91:15-20.
41. deVeber GA. Schwarting GA, Kolodny EH, Kowall NW. Fabry disease: immunocytochemical characterization of neuronal involvement. Ann Neurol 1992;31:409-15.
42. Kaye EM, Kolodny EH, Logigian EL, Ullman MD. Nervous system involvement in Fabry's disease: clinicopathological and biochemical correlation. Ann Neurol 1988;23:505-9.
43. Rosenberg DM, Ferrans VJ, Fulmer JD, Line BR, Barranger JA, Brady RO, et al. Chronic airflow obstruction in Fabry's disease. Am J Med 1980;68:898-905.
44. Nistal M, Paniagua R, Picazo ML. Testicular and epididymal involvement in Fabry's disease. J Pathol 1983;141:113-24.
45. Cole AL, Lee PJ, Hughes DA, Deegan PB, Waldek S, Lachmann RH. Depression in adults with Fabry disease: a common and under-diagnosed problem. J Inherit Metab Dis 2007 Nov 12 [Epub ahead of print].
46. Cable WJ, Kolodny EH, Adams RD. Fabry disease: impaired autonomic function. Neurology 1982;32:498-502.
47. Fellgiebel A, Muller MJ, Ginsberg L. CNS manifestations of Fabry's disease. Lancet Neurol 2006;5:791-5.
48. Mitsias P, Levine SR. Cerebrovascular complications of Fabry's disease. Ann Neurol 1996;40:8-17.
49. Germain DP, Avan P, Chassaing A, Bonfils P. Patients affected with Fabry disease have an increased incidence of progressive hearing loss and sudden deafness: an investigation of twenty-two hemizygous male patients. BMC Med Genet 2002;3:10.
50. Morgan SH, Rudge P, Smith SJ, Bronstein AM, Kendall BE, Holly E, et al. The neurological complications of Anderson-Fabry disease (alpha-galactosidase A deficiency): investigation of symptomatic and presymptomatic patients. Q J Med 1990;75:491-507.
51. Marino S, Borsini W, Buchner S, Mortilla M, Stromillo ML, Battaglini M, et al. Diffuse structural and metabolic brain changes in Fabry disease. J Neurol 2006;253:434-40.
52. Keilmann A. Inner ear function in children with Fabry disease. Acta Paediatr 2003;92:31-2.
53. Ries M, Kim HJ, Zalewski CK, Mastroianni MA, Moore DF, Brady RO, et al. Neuropathic and cerebrovascular correlates of hearing loss in Fabry disease. Brain 2007;130:143-50.
54. Hegemann S, Hajioff D, Conti G, Beck M, Sunder-Plassmann G, Widmer U, et al. Hearing loss in Fabry disease: data from the Fabry Outcome Survey. Eur J Clin Invest 2006;36:654-62.
55. Eng CM, Fletcher J, Wilcox WR, Waldek S, Scott CR, Sillence DO, et al. Fabry disease: baseline medical characteristics of a cohort of 1765 males and females in the Fabry Registry. J Inherit Metab Dis 2007;30:184-92.
56. Mohrenschlager M, Braun-Falco M, Ring J, Abeck D. Fabry disease: recognition and management of cutaneous manifestations. Am J Clin Dermatol 2003;4:189-96.
57. Schiller PI, Itin PH. Angiokeratomas: an update. Dermatology 1996; 193:275-82.
58. Okubo H. Several functional and fluorescein fundus angiographic findings in Fabry's disease. Ophthalmologica 1988;196:132-6.
59. Sodi A, Ioannidis AS, Mehta A, Davey C, Beck M, Pitz S. Ocular manifestations of Fabry disease: data from the Fabry Outcome Survey. Br J Ophthalmol 2006;14:14.
60. Hauser AC, Lorenz M, Sunder-Plassmann G. The expanding clinical spectrum of Anderson-Fabry disease: a challenge to diagnosis in the novel era of enzyme replacement therapy. J Intern Med 2004;255:629-36.
61. Franceschetti AT. Fabry disease: ocular manifestations. Birth Defects Orig Artic Ser 1976;12:195-208.
62. Sher NA, Letson RD, Desnick RJ. The ocular manifestations in Fabry's disease. Arch Ophthalmol 1979;97:671-6.
63. Andersen MV, Dahl H, Fledelius H, Nielsen NV. Central retinal artery occlusion in a patient with Fabry's disease documented by scanning laser ophthalmoscopy. Acta Ophthalmol 1994;72:635-8.
64. Abe H, Sakai T, Sawaguchi S, Hasegawa S, Takagi M, Yoshizawa T, et al. Ischemic optic neuropathy in a female carrier with Fabry's disease. Ophthalmologica 1992;205:83-8.
65. Meroni M, Spisni C, Tazzari S, Di Vito R, Stingone A, Bovan I, et al. Isolated glomerular proteinuria as the only clinical manifestation of Fabry's disease in an adult male. Nephrol Dial Transplant 1997;12:221-3.
66. Branton MH, Schiffmann R, Sabnis SG, Murray GJ, Quirk JM, Altarescu G, et al. Natural history of Fabry renal disease: influence of alpha-galactosidase A activity and genetic mutations on clinical course. Medicine 2002;81:122-38.
67. Peterson JC, Adler S, Burkart JM, Greene T, Hebert LA, Hunsicker LG, et al. Blood pressure control, proteinuria, and the progression of renal disease: the Modification of Diet in Renal Disease Study. Ann Intern Med 1995;15(123):754-62.
68. Ortiz A, Oliveira JP, Waldek S, Warnock DG, Cianciaruso B, Wanner C. Nephropathy in males and females with Fabry disease: cross-sectional description of patients before treatment with enzyme replacement therapy. Nephrol Dial Transplant 2008 Jan 9 [Epub ahead of print].
69. Germain DP, Waldek S, Banikazemi M, Bushinsky DA, Charrow J, Desnick RJ, et al. Sustained, long-term renal stabilization after 54 months of agalsidase beta therapy in patients with Fabry disease. J Am Soc Nephrol 2007;18:1547-57.
70. Fabry RADAR 2007: The Fabry Registry Aggregate Data Annual Report.
71. Thadhani R, Wolf M, West ML, Tonelli M, Ruthazer R, Pastores GM, et al. Patients with Fabry disease on dialysis in the United States. Kidney Int 2002;61:249-55.
72. Ries M, Ramaswami U, Parini R, Lindblad B, Whybra C, Willers I, et al. The early clinical phenotype of Fabry disease: a study on 35 European children and adolescents. Eur J Pediatr 2003;162:767-72.
73. Chimenti C, Pieroni M, Morgante E, Antuzzi D, Russo A, Russo MA, et al. Prevalence of Fabry disease in female patients with late-onset hypertrophic cardiomyopathy. Circulation 2004;110:1047-53.
74. Sachdev B, Takenaka T, Teraguchi H, Tei C, Lee P, McKenna WJ, et al. Prevalence of Anderson-Fabry disease in male patients with late onset hypertrophic cardiomyopathy. Circulation 2002;105:1407-11.
75. Pieroni M, Chimenti C, Ricci R, Sale P, Russo MA, Frustaci A. Early detection of Fabry cardiomyopathy by tissue Doppler imaging. Circulation 2003;22(107):1978-84.
76. Weidemann F, Breunig F, Beer M, Sandstede J, Turschner O, Voelker W, et al. Improvement of cardiac function during enzyme replacement therapy in patients with Fabry disease: a prospective strain rate imaging study. Circulation 2003;108:1299-301.
77. Breunig F, Weidemann F, Strotmann J, Knoll A, Wanner C. Clinical benefit of enzyme replacement therapy in Fabry disease. Kidney Int 2006;69:1216-21.
78. Linhart A, Palecek T, Bultas J, Ferguson JJ, Hrudova J, Karetova D, et al. New insights in cardiac structural changes in patients with Fabry's disease. Am Heart J 2000;139:1101-8.
79. Moon JC, Sheppard M, Reed E, Lee P, Elliott PM, Pennell DJ. The histological basis of late gadolinium enhancement cardiovascular magnetic resonance in a patient with Anderson-Fabry disease. J Cardiovasc Magn Reson 2006;8:479-82.
80. Amann-Vesti BR, Gitzelmann G, Widmer U, Bosshard NU, Steinmann B, Koppensteiner R. Severe lymphatic microangiopathy in Fabry disease. Lymphat Res Biol 2003;1:185-9.
81. Brown LK, Miller A, Bhuptani A, Sloane MF, Zimmerman MI, Schilero G, et al. Pulmonary involvement in Fabry disease. Am J Respir Crit Care Med 1997;155:1004-10.
82. Bierer G, Kamangar N, Balfe D, Wilcox WR, Mosenifar Z. Cardiopulmonary exercise testing in Fabry disease. Respiration 2005;72:504-11.
83. Magage S, Lubanda JC, Susa Z, Bultas J, Karetova D, Dobrovolny R, et al. Natural history of the respiratory involvement in Anderson-Fabry disease. J Inherit Metab Dis 2007;30:790-9.

84. Hoffmann B, Schwarz M, Mehta A, Keshav S. Gastrointestinal symptoms in 342 patients with Fabry disease: prevalence and response to enzyme replacement therapy. Clin Gastroenterol Hepatol 2007;5:1447-53.
85. Manger B, Mengel E, Schaefer RM. Rheumatologic aspects of lysosomal storage diseases. Clin Rheumatol 2007;26:335-41.
86. Cox-Brinkman J, Vedder A, Hollak C, Richfield L, Mehta A, Orteu K, et al. Three-dimensional face shape in Fabry disease. Eur J Hum Genet 2007;15:535-42.
87. Ries M, Moore DF, Robinson CJ, Tifft CJ, Rosenbaum KN, Brady RO, et al. Quantitative dysmorphology assessment in Fabry disease. Genet Med 2006;8:96-101.
88. Lien YH, Lai LW. Bilateral femoral head and distal tibial osteonecrosis in a patient with Fabry disease. Am J Orthop 2005;34:192-4.
89. Germain DP, Benistan K, Boutouyrie P, Mutschler C. Osteopenia and osteoporosis: previously unrecognized manifestations of Fabry disease. Clin Genet 2005;68:93-5.
90. Mersebach H, Johansson JO, Rasmussen AK, Bengtsson BA, Rosenberg K, Hasholt L, et al. Osteopenia: a common aspect of Fabry disease: Predictors of bone mineral density. Genet Med 2007;9:812-8.
91. Eng CM, Germain DP, Banikazemi M, Warnock DG, Wanner C, Hopkin RJ, et al. Fabry disease: guidelines for the evaluation and management of multi-organ system involvement. Genet Med 2006;8: 539-48.
92. Grewal RP. Psychiatric disorders in patients with Fabry's disease. Int J Psychiatry Med 1993;23:307-12.
93. Sadek J, Shellhaas R, Camfield CS, Camfield PR, Burley J. Psychiatric findings in four female carriers of Fabry disease. Psychiatr Genet 2004;14:199-201.
94. Tsutsumi O, Sato M, Sato K, Mizuno M, Sakamoto S. Early prenatal diagnosis of inborn error of metabolism: a case report of a fetus affected with Fabry's disease. Asia Oceania J Obstet Gynaecol 1985;11:39-45.
95. Vedder AC, Strijland A, vd Bergh Weerman MA, Florquin S, Aerts JM, Hollak CE. Manifestations of Fabry disease in placental tissue. J Inherit Metab Dis 2006;29:106-11.
96. Ramaswami U, Whybra C, Parini R, Pintos-Morell G, Mehta A, Sunder-Plassmann G, et al. Clinical manifestations of Fabry disease in children: data from the Fabry Outcome Survey. Acta Paediatr 2006;95: 86-92.
97. Kint JA. Fabry's disease: alpha-galactosidase deficiency. Science 1970; 167:1268-9.
98. Chamoles NA, Blanco M, Gaggioli D. Fabry disease: enzymatic diagnosis in dried blood spots on filter paper. Clin Chim Acta 2001;308: 195-6.
99. Skoog WA, Beck WS. Studies on the fibrinogen, dextran and phytohemagglutinin methods of isolating leukocytes. Blood 1956;11:436-54.
100. Coelho JC, Giugliani R. Fibroblasts of skin fragments as a tool for the investigation of genetic diseases: technical recommendations. Gen Mol Biol 2000;23:269-71.
101. Desnick RJ, Brady R, Barranger J, Collins AJ, Germain DP, Goldman M, et al. Fabry disease, an under-recognized multisystemic disorder: expert recommendations for diagnosis, management, and enzyme replacement therapy. Ann Intern Med 2003;138:338-46.
102. Linthorst GE, Vedder AC, Aerts JM, Hollak CE. Screening for Fabry disease using whole blood spots fails to identify one-third of female carriers. Clin Chim Acta 2005;353:201-3.
103. Kusiak JW, Quirk JM, Brady RO. Purification and properties of the two major isozymes of alpha-galactosidase from human placenta. J Biol Chem 1978;253:184-90.
104. Nakao S, Takenaka T, Maeda M, Kodama C, Tanaka A, Tahara M, et al. An atypical variant of Fabry's disease in men with left ventricular hypertrophy. N Engl J Med 1995;333:288-93.
105. Auray-Blais C, Cyr D, Ntwari A, West ML, Cox-Brinkman J, Bichet DG, et al. Urinary globotriaosylceramide excretion correlates with the genotype in children and adults with Fabry disease. Mol Genet Metab 2007 Nov 16 [Epub ahead of print].
106. Desnick RJ, Bernstein HS, Astrin KH, Bishop DF. Fabry disease: molecular diagnosis of hemizygotes and heterozygotes. Enzyme 1987;38: 54-64.
107. Miller SA, Dykes DD, Polesky HF. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res 1988; 16:1215.
108. Eng CM, Resnick-Silverman LA, Niehaus DJ, Astrin KH, Desnick RJ. Nature and frequency of mutations in the alpha-galactosidase A gene that cause Fabry disease. Am J Hum Genet 1993;53:1186-97.
109. Sanger F, Nicklen S, Coulson AR. DNA sequencing with chain-terminating inhibitors. 1977. Biotechnology 1992;(24):104-8.
110. Hilz MJ. Evaluation of peripheral and autonomic nerve function in Fabry disease. Acta Paediatr Suppl 2002;91:38-42.
111. Argoff CE, Barton NW, Brady RO, Ziessman HA. Gastrointestinal symptoms and delayed gastric emptying in Fabry's disease: response to metoclopramide. Nucl Med Commun 1998;19:887-91.
112. Kelly MM, Leigh R, McKenzie R, Kamada D, Ramsdale EH, Hargreave FE. Induced sputum examination: diagnosis of pulmonary involvement in Fabry's disease. Thorax 2000;55:720-1.
113. Shelley ED, Shelley WB, Kurczynski TW. Painful fingers, heat intolerance, and telangiectases of the ear: easily ignored childhood signs of Fabry disease. Pediatr Dermatol 1995;12:215-9.
114. Tahir H, Jackson LL, Warnock DG. Antiproteinuric therapy and Fabry nephropathy: sustained reduction of proteinuria in patients receiving enzyme replacement therapy with agalsidase-beta. J Am Soc Nephrol 2007;18:2609-17.
115. Eng CM, Banikazemi M, Gordon RE, Goldman M, Phelps R, Kim L, et al. A phase 1/2 clinical trial of enzyme replacement in Fabry disease: pharmacokinetic, substrate clearance, and safety studies. Am J Hum Genet 2001;68:711-22.
116. Eng CM, Guffon N, Wilcox WR, Germain DP, Lee P, Waldek S, et al. Safety and efficacy of recombinant human alpha-galactosidase A replacement therapy in Fabry's disease. N Engl J Med 2001;345:9-16.
117. Ohshima T, Murray GJ, Swaim WD, Longenecker G, Quirk JM, Cardarelli CO, et al. Alpha-galactosidase A deficient mice: a model of Fabry disease. Proc Natl Acad Sci U S A 1997;94:2540-4.
118. Wang A, Ioannou Y, Zeidner K. Fabry disease: generation of a mouse model with alpha-galactosidase A. Am J Hum Genet 1996;59.
119. Ioannou YA, Zeidner KM, Gordon RE, Desnick RJ. Fabry disease: preclinical studies demonstrate the effectiveness of alpha-galactosidase A replacement in enzyme-deficient mice. Am J Hum Genet 2001;68:14-25.
120. Thurberg BL, Randolph Byers H, Granter SR, Phelps RG, Gordon RE, O'Callaghan M. Monitoring the 3-year efficacy of enzyme replacement therapy in Fabry disease by repeated skin biopsies. J Invest Dermatol 2004;122:900-8.
121. Wilcox WR, Banikazemi M, Guffon N, Waldek S, Lee P, Linthorst GE, et al. Long-term safety and efficacy of enzyme replacement therapy for Fabry disease. Am J Hum Genet 2004;75:65-74.
122. Banikazemi M, Bultas J, Waldek S, Wilcox WR, Whitley CB, McDonald M, et al. Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. Ann Intern Med 2007;146:77-86.
123. Wraith JE, Tylki-Szymanska A, Guffon N, Lien YH, Tsimaratos M, Vellodi A, et al. Safety and efficacy of enzyme replacement therapy with agalsidase beta: an international, open-label study in pediatric patients with Fabry disease. J Pediatr, in press.
124. Hilz MJ, Brys M, Marthol H, Stemper B, Dutsch M. Enzyme replacement therapy improves function of C-, Adelta-, and Abeta-nerve fibers in Fabry neuropathy. Neurology 2004;62:1066-72.
125. Banikazemi M, Ullman T, Desnick RJ. Gastrointestinal manifestations of Fabry disease: clinical response to enzyme replacement therapy. Mol Genet Metab 2005;85:255-9.
126. Spinelli L, Pisani A, Sabbatini M, Petretta M, Andreucci MV, Procaccini D, et al. Enzyme replacement therapy with agalsidase beta improves cardiac involvement in Fabry's disease. Clin Genet 2004;66:158-65.
127. Kalliokoski RJ, Kantola I, Kalliokoski KK, Engblom E, Sundell J, Hannukainen JC, et al. The effect of 12-month enzyme replacement therapy on myocardial perfusion in patients with Fabry disease. J Inherit Metab Dis 2006;29:112-8.
128. Hollak CE, Vedder AC, Linthorst GE, Aerts JM. Novel therapeutic targets for the treatment of Fabry disease. Expert Opin Ther Targets 2007; 11:821-33.